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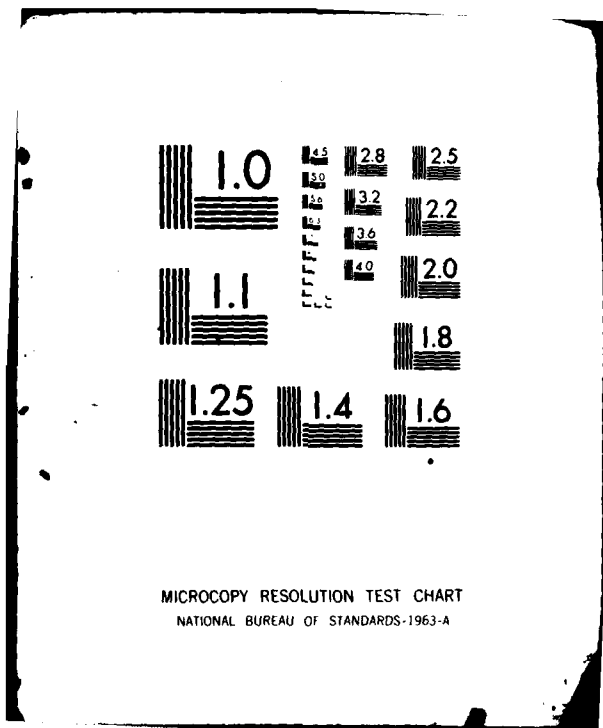
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NINTH INTERNATIONAL CONFERENCE ON SARCOIDOSIS

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15 OCTOBER 1981

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) In this report on the most recent international conference on sarcoidosis the author discusses the current status of sarcoidosis research and the latest developments in clinical treatment as they were related at the conference. He also refers to the differing opinions that were presented about diagnosis and treatment of the disease, as well as recommendations that were made as to future areas of study.		

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NINTH INTERNATIONAL CONFERENCE ON SARCOIDOSIS

From August 31 through September 4, 1981, the Paris-Sheraton Hotel on Montparnasse was the setting of the Ninth International Conference on Sarcoidosis and other Granulomatous Disorders; the first such conference was held in 1958. In sessions arranged so that all of the 400 participants from 37 countries could hear all the papers, there were 86 oral presentations, dealing with current research in this field, about 15 "state of the art" and summary talks, and over 125 posters which highlighted current work. The languages of the conference were French and English, with smoothly working simultaneous translation. Discussions were quite lively. Among the oral scientific talks, 28 were from France and 12 were from Japan.

The granuloma is a microscopic pathologic lesion that can be found in any tissue or organ of the body. It is a collection of cells of the monocyte-macrophase series, including epithelioid cells and lymphocytes. It is a hallmark of chronic inflammation and is found in a wide variety of diseases, ranging from infections such as tuberculosis, leprosy, syphilis, and those caused by fungi and protozoa, through reactions to inhaled toxic substances, to disorders that seem to represent aberrations of the immune system, such as Crohn's disease, primary biliary cirrhosis, and systemic lupus erythematosus. Sarcoidosis falls into the last-named category.

Research on sarcoidosis is a microcosm of biomedical research in general. Immunology, biochemistry, cellular biology, nuclear applications, pulmonary physiology, and epidemiology were the fields dominating the conference. Since sarcoidosis affects the lungs most frequently, and at times very seriously, most of the participants were pulmonary physicians. There were numerous papers on using new immunologic and biochemical information for making the diagnosis of sarcoidosis, and one session on therapy.

The symptoms and signs of sarcoidosis range from incidental X-ray findings in individuals who feel well, to severe respiratory incapacity and death. They depend on the tissues involved, the most common being lymph nodes, lungs, skin, eyes, liver and spleen, bone, heart, and the salivary and lacrimal glands. Historically, physicians have made this diagnosis on the basis of clinical features, including several distinctive syndromes: the exclusion of known agents that cause granulomatous disorder; a negative tuberculin skin test (anergy), and a positive Kveim-Siltzbach skin test. (The Kveim test antigen, which is not commercially available, is prepared from human sarcoid tissue. Following injection of this material into the skin of the patient, the skin nodule is biopsied in four to six weeks. A positive test is the finding of typical sarcoid granuloma formation.)

In the US, sarcoidosis is considered to be overwhelmingly a disease of blacks. In Harlem, the incidence is approximately 50 per 100,000 population. In some parts of the world, however, this level of frequency

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is reached in white populations. One of the fascinating aspects of the disease is its variable geographic distribution.

At the congress, the epidemiology of sarcoidosis was reviewed and some new information added. There was considerable criticism of current data-gathering techniques, and there were also recommendations for more valid studies. Recognition of the disease is variable; for example, sarcoidosis is detected more frequently where chest X-ray screening is more widespread. In both Japan and Italy sarcoidosis is more common in colder, northern latitudes, while in the US it is more common in southern, rural areas.

Theories on the cause of sarcoidosis relating it to soil types and pine pollen have been abandoned. The need for collaborative studies between institutions and countries was stressed, and emphasis was placed on the need for national registers of the disease and on standardized criteria for diagnosis and epidemiologic hypotheses developed in advance.

There is a particularly high incidence of sarcoidosis in Denmark and Sweden (and, strangely, a much lower incidence in Norway and Finland). A study of Danish military personnel revealed an incidence of about 50 cases per 100,000 population. An impromptu report from the People's Republic of China indicated that over 100 cases have been reported in the medical literature of that country, but there is no basis as yet for establishing incidence figures. Poster sessions on the incidence of the disease came from Central Europe, France, Rumania, Algeria, Malaysia, Spain (1.2 per 100,000—very low), and Brazil (0.2 per 100,000—very, very low).

The racial differences in the US are largely unexplained. A genetic-epidemiologic study from Johns Hopkins University Medical School revealed an association of sarcoidosis with a specific HLA-type (tissue antigen) in blacks, as well as a specific inherited immunoglobulin type. Previously, an association had been noted between sarcoidosis and a specific HLA-type in whites. In the discussion, it was pointed out that quite different genetic markers are associated with sarcoidosis in Japan.

A. Teirstein, (Mt. Sinai Schl of Med., New York City) a colleague of the late Louis Siltzbach, one of the charter members of these conferences, suggested that US clinicians should relinquish the idea that sarcoidosis is a disease of blacks. In a poster, these pulmonary physicians showed the marked disparity between patients attending a clinic and those under the care of the same physicians in their private offices. Of 110 biopsy-proven cases seen in private offices, 89 (81%) were caucasian, 18 (16%) were black, and 3 (3%) were hispanic. In the clinic population, of 104 patients, 59 (57%) were black, 32 (31%) were caucasian, and 13 (12%) were hispanic. these data emphasize the socio-economic influences that characterize patient populations and that lead to disparity in perceived ethnic distributions.

R. Crystal, (Nat. Inst. of Health, Bethesda, Md), provided a comprehensive "state of the art" on the pathogenesis of sarcoidosis, with emphasis on immunologic aspects. Confining discussion to the lung, he pointed out that the granuloma there is preceded by alveolitis, an inflammatory reaction in the terminal air sacs. Granuloma formation may be followed by fibrosis (scarring) which is the pathologic feature leading to loss of respiratory function. Numerous papers and lively discussion dealt with this sequence of events.

Alveolitis is detected by broncho-alveolar lavage (BAL), a procedure receiving considerable current attention. In this technique, a fiberoptic bronchoscope is inserted into a segment of the lung air passages, and 100 ml of saline are introduced to wash out cells and chemical mediators. About 50 to 70 ml of fluid are recovered for analysis. (This procedure is relatively innocuous and not as discomfoting as it sounds).

Normally, 90% of the cells recovered are alveolar macrophages, and less than 10% are lymphocytes. In sarcoidosis, there is a shift to lymphocytes, ranging from 20 to 70%. These lymphocytes are of the T-cell variety. There is an absolute increase in all types of cells: 16 times for T-lymphocytes, 3 times for alveolar macrophages and 2 times for B-lymphocytes. Activated T-cells produce numerous chemical mediators (lymphokines, chemotactic factor, leukocyte-inhibiting factor) which, in turn, stimulate activity of the alveolar macrophages. Many papers and much discussion concerned the process of granuloma formation, the stimulation of fibrosis, and how the cells that are recovered in BAL reflect the granulomatous process in the disease.

Sophisticated immunologic studies on these altered cell populations and their functional significance were contradictory. New methods, as in all contemporary science, offer new prospects. The use of monoclonal antibodies appears to be a very promising technique for developing new information in this field.

During the conference, four previously appointed Commissions gave reports, the first of which was on the definition of sarcoidosis. After two days of intense immunologic discussion, the first line of the report of Commission I would certainly appear justified: "Sarcoidosis is a multi-system granulomatous disease of unknown etiology characterized by an enhanced cellular immune process at the sites of involvement."

Commission I further provided minimal criteria for diagnosis, including histologic evidence, consistent clinical features, and the exclusion of known agents that cause granulomatous disorders.

Commission II had the onerous task of recommending criteria for "activity" of sarcoid disease. This was a subject of considerable debate and the theme of many of the papers. (The recommendations of the four commissions are by no means final. Participants were invited to make their views known so that modifications might be introduced before the ultimate publication of the reports).

The report of Commission II gave indices of activity under five headings: clinical indices, pathologic indices, immunologic signs, biologic changes, and those revealed by complementary techniques.

The *clinical indices* listed by Lebacqz were uveitis, erythema nodosum, polyarthropathy, dactylitis, granulomatous infiltration of a scar, myopathy/neuropathy, salivary and lacrimal gland enlargement, lymphadenopathy and splenomegaly. Quite a stir went through the gathering when this list was shown, principally because there was no reference to pulmonary disease. Dr. James (Royal Northern Hospital, London) a very active participant as well as a principal organizer and commission member, pointed out that lung findings, bone cysts, and other clinical features of sarcoidosis were not signs of "activity." The audience did not seem convinced.

The *pathologic indices* of activity were listed as persistence of mononuclear cell infiltration and granuloma formation. The question was raised as to whether "without fibrosis" should be added, referring to the end-stage of the disease in the lung.

Immunologic signs proposed are activation of T- and B-lymphocytes and macrophages at sites of disease, including BAL, and evidence of anergy in blood and skin (e.g., negative tuberculin test).

Biologic changes listed for activity included an elevated serum level of angiotensin-converting enzyme (ACE—more on this later), elevated circulating immune complexes (CIC) and positive Kveim-Siltzbach test.

Finally, the *complementary techniques* that reveal activity were fluorescein ocular angiography, and gallium-67 lung scanning (more on this later).

"What about chest X-rays and pulmonary function tests?" asked several participants. M. Turner-Warwick, (Brompton Hospital, London) asked how these interesting new tests, referring particularly to ACE and ⁶⁷Ga scanning, have been validated. Indeed, many of the conference papers dealt with these subjects, showing considerably less than 100% specificity and/or sensitivity for sarcoidosis. She wondered whether the commission was not engaged in a "circular argument."

Many of the new tests are invasive and/or very costly. Many are simply not available outside large medical centers. Clinicians wondered what would be required for a definitive diagnosis and a determination of activity of the disease.

ACE is an enzyme normally found on the endothelium of the lung and, to a lesser extent, elsewhere (kidney). It is essential to the function of two normal humoral feedback loops—in the conversion of angiotensin I to angiotensin II, and in the inactivation of brady kinin. ACE probably has other, as yet unknown, functions, but it is named for its role in the renin-angiotensin-aldosterone system, a long-term regulator of blood pressure and sodium excretion.

ACE is of great clinical as well as investigative interest. A new drug, captopril, released for use in the treatment of hypertension, has as its mechanism of action the inhibition of ACE. This action prevents the formation of angiotensin II in the lung, eliminating a powerful circulating vasoconstrictor. The failure to inactivate brady kinin results in increasing levels of a vasodilator. These effects may combine to lower an elevated blood pressure.

Several years ago, it was discovered fortuitously that serum ACE levels are elevated in sarcoidosis. The obvious need for a reliable biochemical marker in this disease has stimulated a large output of research on the relationship of serum, tissue, and BAL levels of ACE to other evidences of sarcoidosis.

There were 19 oral presentations and 11 posters on current ACE investigations, including the effects of captopril in granulomatous disorders. Various degrees of correlation with other markers and tests were reported. Clearly, ACE is helpful in monitoring the course of sarcoidosis, but there was considerable disagreement over the likelihood of false positive and false negative results, as well as about what levels are to be considered abnormal, what body fluids or tissues should be tested for ACE activity, and the ACE assay methodology. ACE activity is high in other diseases, notably diabetes mellitus, particularly when there is renal angiopathy, and primary biliary cirrhosis, another important granulomatous disorder.

Where does ACE come from? The implication was that it is produced by cells in the granuloma, and there was evidence that ACE activity correlates with the total granuloma volume. More work is needed in this promising area.

The ^{67}Ga scanning method received equal attention, with perhaps slightly more usefulness assigned to it. Injected ^{67}Ga is taken up by the macrophages and produces a visual image of the distribution of sarcoid in lungs and other organs and tissues. Together with the results of BAL, ^{67}Ga scanning was thought by some to correlate well with "high density" alveolitis, although it is expensive and not without risk.

After discussing the markers of activity of sarcoidosis—including tests not reviewed in this brief summary, such as lysozymes, CIC, collagenase, beta₂ microglobulins, kappa and lambda chains—James labeled as "front runners" the Kveim test, serum ACE, and BAL.

Commission II also dealt with the chest radiographic findings in sarcoidosis and offered a classification of four "types" rather than "stages," the previously used term which implied erroneously that patients progress from Stage I to Stage II and so on. Type 0 is a clear chest X-ray; Type I shows lymph node enlargement (hilar adenopathy) alone; Type II shows adenopathy plus parenchymal lung changes; and Type III shows the lung changes alone.

In a summary talk, C. Voisin (Pasteur Inst., Lille, France) pointed out that, in general, the prognosis in sarcoidosis is favorable. The disease evolves over a long period, with deterioration of pulmonary function due to fibrosis not the usual outcome. He criticized the work presented at this meeting for still not showing the changes that were occurring in tissues and airways during the progression towards fibrosis.

In a similar view, Turner-Warwick noted that the problems of activity and new markers in sarcoidosis had been "flogged to death" and that "which is best" among ACE, BAL, ⁶⁷Ga scanning, etc., is a "non-question." Markers are not picking up all the cases, but no clinical definition of activity had been offered by the congress. She pointed out the importance of measuring activity and emphasized that treatment at the right time might prevent premature chronic disability and death. It appeared to her that the granuloma had a higher association with the development of fibrosis than did alveolitis. (This last point was supported by W. Jones-Williams (Welsh Nat. School of Medicine, Cardiff) who noted that histologic examination of the lungs of patients with fibrosis always revealed evidences of granuloma, but that alveolitis could rarely be seen).

The report of Commission III, headed by H. Hosada and R. Mikami (Japan Sarcoidosis Committee, Tokyo) provided guidelines for therapeutic trials. The principal effective therapy in sarcoidosis has been adrenal corticosteroids. Larger and longer controlled studies relating to daily and alternate-day treatment schedules in carefully selected patients with valid diagnoses are needed. Multi-institutional and international trials are desirable.

R. De Remee (Mayo Clinic, Rochester, MN) presented the results of a survey on the treatment of sarcoidosis conducted by questionnaire among 275 US pulmonary physicians. Most of these physicians found steroids helpful, but there was disagreement on the indications for treatment. Less than 1% treated patients with "Stage I" disease (hilar adenopathy only). Administration of prednisone, in doses of 40 mg per day or 40 mg every other day, was the most favored treatment. Patients were treated as long as the disease was "active" (undefined) by 45% of physicians, and for an arbitrary duration by 55%.

De Remee pointed out that alternate-day regimens have been shown to be as effective as daily steroid doses and, of course, they are accompanied by fewer side effects. Spontaneous remissions of sarcoidosis are common and must be taken into account when evaluating therapy. The granulomatous phase of the disease is potentially reversible, while the fibrotic phase is not. De Remee offered the conference a modified classification of patients with sarcoidosis based on radiologic "stage" pulmonary function and an activity index (serum ACE, BAL, and ⁶⁷Ga scanning).

James suggested that prednisolone was the better steroid to use in these patients. Prednisone must be converted to prednisolone in the liver, and sarcoid patients often have impaired hepatic function.

Commission IV had the responsibility of defining and classifying "other granulomatous disorders." As listed and classified, these include *infections*, *chemical*-induced pulmonary disease (beryllium, zirconium, silica), *immunologic* aberrations (some of which have been named previously), *enzyme defects*, some *neoplasms*, extrinsic allergic alveolitis (e.g., farmer's lung, bird fancier's lung, bagassosis) and *miscellaneous* disorders such as sebaceous cyst and tissue injury due to radiotherapy. A call was issued for the addition of items to this list in the hope that they will help in elucidating the pathogenesis of sarcoidosis and the search for more effective therapy.

Among the diseases, there were papers on schistosomiasis, leprosy, Crohn's disease, and bird fancier's disease. However, in keeping with previous conferences, one disorder was selected for fuller discussion. Thus, six papers and two general talks were devoted to histiocytosis X, a spectrum of disease that medical workers will recognize as comprising eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease. These disorders are listed here in the order of their mortality rates—64% in Letterer-Siwe disease, which is characterized by widespread visceral involvement in children. This proliferative granulomatous disease is little understood and is characterized by some as neoplastic.

The sarcoid "movement," as it was referred to by one discussant, is obviously very much alive. An extraordinary range of biomedical disciplines is working in this movement and the work is contemporary, sophisticated, and relevant to the full spectrum of human disease. Immunology has been tritely described as the "cutting edge" of modern biomedical research and it dominates this field, much as it dominates other large areas of research in human disease, such as cancer.

The conference provided a classic picture of the manner in which advances are slowly made in medicine. There could be no "conclusions." Small bits of information were developed, synthesized into larger hypotheses, and then found wanting in the effort to understand the disease process. The Tenth International Conference on Sarcoidosis, scheduled to be held in Baltimore in 1983, will, no doubt, again be dominated by immunologists, biochemists, and cellular biologists, adding more small pieces to this large, as yet unrecognizable picture.

